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Towards robust parvo virus filtration processes: Influence of pre-filtration, membrane structure, membrane surface properties and mode of operation

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In 1984, HIV was determined as the root cause for AIDS. Viral infections transmitted by blood products generated an urgent need for virus clearance technologies. Membrane based virus removal was introduced in 1989 by Asahi Kasei Corporation, significantly enhancing virus safety in blood products and other biopharmaceuticals. Today, size based removal of viruses is a standard step in most biopharmaceutical productions and regarded as the most robust virus clearance technology available. Virus retentive filters are usually operated in a dead-end mode, designed to reject virus particles and to yield >98% product recovery for proteins of less than 170 kDa. Virus filtration feed streams generally have high purity and high product concentrations. Decrease in permeate flux during virus filtration, which reduces filter capacity, is often due to fouling by hydrophobic protein variants or small aggregates present in the feed stream. Flat sheet virus membranes typically feature a multi-layer porous polymer structure that is uniquely designed to provide the needed virus clearance while allowing high recovery of the desired protein product. The base polymer of these membranes must resist process-induced physical and chemical wear and is therefore generally a rather hydrophobic material. As the knowledge of viruses and their removal by filtration grew, respective regulatory guidelines and goals were developed that strongly promoted virus clearance technologies.

In a first part, we will present the technological milestones in the evolution of membrane based virus removal, rationalizing the developments using today's understanding. Published as well as novel unpublished data form the basis for this scientific presentation. The progress in membrane throughput and capacity will be related to advances in membrane structure and membrane surface properties as well as to the optimization of feed stream solution properties, also through the use of adsorptive pre-filters. The impact of virus membrane interactions as well as the influence of pressure fluctuations and challenge levels on virus removal will be demonstrated.

In a second part, we will present how a novel virus filter for blood and plasma products was developed. When heterogeneous products such as IgG from pooled blood samples is filtered, protein adsorption on the hydrophobic base polymer surface are the main cause for flux decay. By grafting a hydrogel layer on the membrane inner surface one can significantly reduce protein adsorption and thus increase membrane performance. The surface properties are changed while retaining the stability of the base membrane. High throughput membrane characterization techniques were used to accelerate membrane development and will be presented. Adsorption isotherms of IgG subfractions to virus filters are correlated to membrane filtration performance of the same subfractions. The objective of this second part of the paper is to demonstrate how membrane structure, membrane surface properties, operating mode (constant pressure vs. constant flow) and pre-filtration affect overall filtration performance.

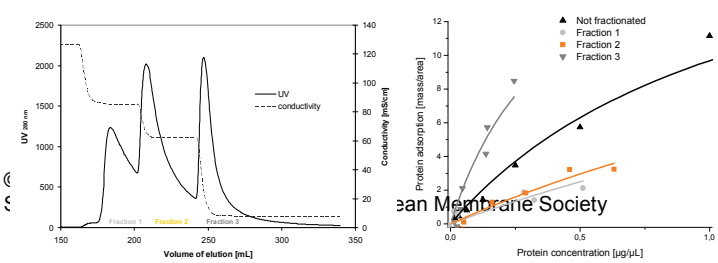

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Fig 1: HIC fractionation of IVIG

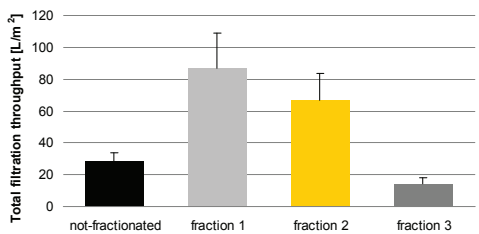

Fig 2: Adsorption isotherms

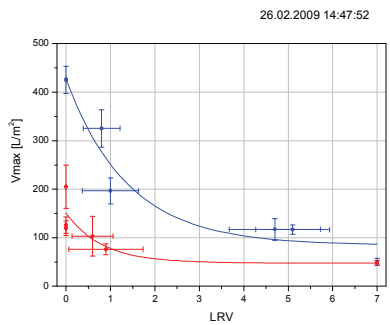

Fig 3: Filtration capacity IVIG fractions

Fig 4: Filtration performance with and without surface modification

Keywords: Parvo virus filtration, Surface modification, Adsorptive pre-filtration